CASE STUDY

Biodegradable stent placement before neoadjuvant chemoradiotherapy as a bridge to surgery in patients with locally advanced esophageal cancer

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Dysphagia is the most common presenting symptom in patients with esophageal malignancy and contributes significantly to weight loss and malnourishment. An increasing number of patients with locally advanced esophageal cancer undergo treatment with neoadjuvant chemoradiotherapy (CRT) before surgery because this has been shown to improve survival.[1] Neoadjuvant CRT is, however, associated with acute inflammation and edema of the esophageal mucosa, which could increase symptoms of dysphagia and potentially further jeopardize nutritional status.[2]

There are various options for nutritional support during neoadjuvant CRT, including nasal-enteral tube feeding, laparoscopic jejunostomy, and total parenteral nutrition. None of these options relieves dysphagia. Therefore, based on the good results of self-expandable stent placement in the palliative setting, self-expandable stents were introduced as a bridge to surgery during neoadjuvant treatment. Fully covered, self-expandable, metal and plastic stents (FSEMS and FSEPS) have been used with good results, but this is at the expense of additional endoscopic procedures either to remove a migrated stent or to extract the stent before surgery.[3-6] In addition, SEMSs may hamper dose planning of radiotherapy because of backscatter on CT.[7]

Recently, biodegradable stents have been developed to treat refractory benign esophageal strictures.[8,9] These biodegradable stents have the potential to refute the problems encountered with FSEMSs and FSEPSs; migration is less likely because the stent is uncovered, and removal is not necessary because the stent will be resolved at the time of esophagectomy. The aim of this study was to evaluate safety and efficacy of biodegradable stent placement before neoadjuvant CRT as bridge to surgery in patients with locally advanced esophageal cancer and dysphagia.

PATIENTS AND METHODS

This study was designed as a prospective feasibility study in 2 academic hospitals, the Academic Medical Center in Amsterdam and the University Medical Center Utrecht (registered under number NTR2928 in the Dutch Trial Register). The medical ethics committees of both centers approved the protocol, and written informed consent was obtained from each patient.

Patients

Based on historical data regarding the number of esophageal cancer patients presenting in our centers, we aimed to include 16 patients in 2 years. All consecutive patients with resectable esophageal carcinoma scheduled for neoadjuvant CRT and those with complaints of dysphagia for

Abbreviations: CRT, chemoradiotherapy; FSEMS, fully covered, self-expandable, metal stent; FSEPS, fully covered, self-expandable, plastic stent; SEMS, self-expandable metal stent.

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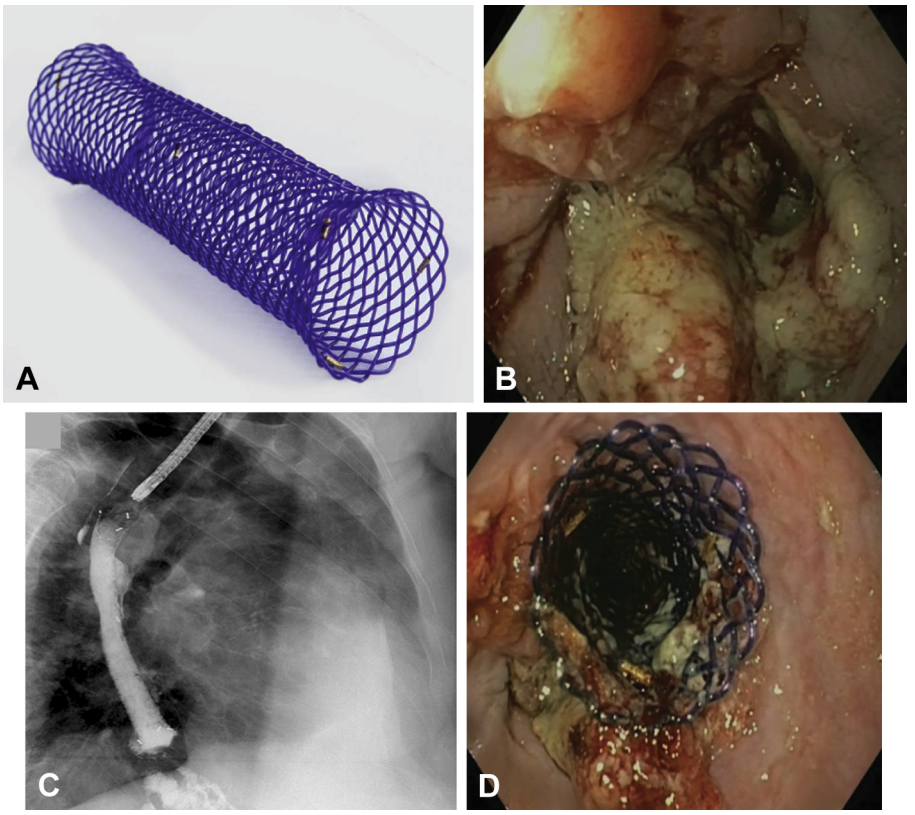

Figure 1. A, Picture of the Ella-SX biodegradable stent. **B,** Obstructing adenocarcinoma in the distal esophagus. **C,** Fluoroscopic control of stent deployment with radiopaque contrast agent. **D,** Endoscopic control of stent position.

solid food (grade ≥ 2 [scale 0-4])[10] were considered for inclusion. Exclusion criteria were as follows: tumor length of >10 cm, tumor growth within 5 cm of the upper esophageal sphincter, tumor extension into the stomach of more than 5 cm, a deep ulcer, a fistula, or no significant stricture.

For safety reasons, a "layered" inclusion scheme was used for the first 5 patients. This dictated that inclusion was open only if the previous patient had completed CRT without the occurrence of any stent-related serious adverse event, and, therefore, there was a waiting period of 5 weeks (ie, CRT duration) after inclusion of 1 of the first 5 patients before a next patient could be included This strategy was chosen because of the high serious adverse event rate in a previous study investigating biodegradable stent placement combined with single-dose brachytherapy for palliation of dysphagia.[11] After these initial 5 patients, inclusion was without restrictions.

All eligible patients who were not included in the study were treated with placement of a nasoduodenal feeding tube in combination with surveillance by a dietician or by dietary surveillance alone, depending on patient nutritional status.

Materials and intervention

The Ella-SX biodegradable stent (Ella-CS; Hradec Kralove, Czech Republic) is Conformité Européenne approved and has an indication for use in benign strictures (peptic, anastomotic, caustic, and post-irradiation) (Fig. 1). The stent is uncovered and available in lengths of 60, 80, and 100 mm, and, for this study, only stents with body diameters of 18 mm and flare diameters of 23 mm were used. Radiopaque markers at both ends and at the middle of the stent enable fluoroscopic visualization. The stent is made of woven polydioxanone monofilaments, and disintegrates 11 to 12 weeks after implantation. The stent is mounted on a delivery system shortly before implantation; the outer diameter of the delivery system is 9.4 mm. Stent placement was done with the patients under conscious or deep sedation. If a pediatric endoscope (Olympus XP-160; Olympus Medical Systems Europe, Hamburg, Germany, or similar) could not pass the stricture, a Savary bougie dilation was performed up to 10 mm to facilitate safe insertion of the delivery system. The length of the stricture was measured endoscopically. The proximal part of the stricture was marked with intramucosal injection of a radiopaque contrast agent to facilitate accurate stent placement under radiologic guidance. A guidewire was positioned, and the delivery device was introduced over the guidewire. The stent was placed with proximal and distal margins of at least 1.5 cm of the stricture. The correct position of the stent was confirmed with fluoroscopy and/or endoscopy (Fig. 1). All patients, with the stent traversing the lower esophageal sphincter, received a proton pump inhibitor after the procedure (omeprazole 40 mg daily).

Stent placement was performed before the start of neoadjuvant CRT. All patients received the same type of neoadjuvant CRT for a period of 5 weeks.[2] Surgery was scheduled 4 to 6 weeks after completion of neoadjuvant CRT, consequently, the stents should have been fully disintegrated at the time of surgery.

Follow-up and study endpoints

After we obtained informed consent, patients' demographics and clinical characteristics including dysphagia score were registered by the research fellow (baseline). Procedure-related data were recorded by the research fellow or treating physician. The research fellow performed follow-up by telephone on day 1, 2, and 7 and weekly thereafter until the day of surgery or withdrawal by using a standardized questionnaire focusing on dysphagia, weight changes, and adverse events.

The following outcomes were analyzed: 30-day mortality and morbidity after stent placement; intervention-related serious adverse events including perforation, hemorrhage requiring blood transfusion with at least 2 units of packed cells, severe retrosternal pain requiring treatment with intravenous opiates for over 48 hours, or any other intervention-related event requiring admission to the intensive care unit or resulting in surgical intervention or death; intervention-related adverse events; technical success, defined as successful stent placement and deployment at the site of the stricture; clinical success, defined as improvement of the dysphagia score within 1 week after stent placement; improvement of the dysphagia score during total follow-up; and weight changes measured in percentages of kilograms of bodyweight.

Statistical analysis

This feasibility study is descriptive by nature; therefore, no formal power calculation was performed. Descriptive statistics were used for data of all included patients (intention to treat). A paired samples *t* test was used to assess improvements from baseline for dysphagia scores. Statistics were performed with the SPSS (version 20.0) software package (SPSS, Chicago, Ill). Statistical significance was set at $P < .05$.

RESULTS

Between November 2011 and December 2013, 35 patients were screened for inclusion. The study was terminated prematurely after inclusion of 10 patients, because of difficult patient accrual. Because of the "layered" inclusion, 15 patients who fulfilled inclusion criteria could not be included because they presented while CRT of 1 of the first 5 patients was still ongoing. Furthermore, tumor bleeding occurred in 1 patient for which radiotherapy was performed before informed consent for the study, and 9 patients declined to participate in the study for various reasons (ie, satisfied with nasoduodenal feeding tube [n = 2], afraid of stent-related adverse events [n = 7]). Baseline patient demographics, clinical characteristics, and procedural information are reported in Table 1.

TABLE 1. Baseline patient demographics, clinical characteristics, and procedural information

Age, mean (SD), y	68 (7.7)
Male:female, no.	7:3
ASA score, no.	
1	1
2	7
3	2
Dysphagia score, mean (SD)	3 (0.67)
Body mass index (kg/m^2), no.	
<18.5	1
18.5-20	1
>20	8
Tumor type, no.	
Adenocarcinoma	9
Squamous cell carcinoma	1
Tumor location, no.	
Mid-esophagus	1
Distal esophagus	5
Gastroesophageal junction	4
Tumor length, mean (SD), cm	4.9 (1.7)
cTNM-stage,* no.	
I	2
II	4
III	4
Pre-dilation, no.	2
Stent length, no., mm	
60	2
80	4
10	4
Time between stent-placement and start of chemoradiotherapy, median (range), d	15 (12-25)

SD, Standard deviation; *ASA score*, American Society of Anesthesiologists Physical Status Classification System score.
*Clinical tumor-node-metastasis stage according to American Joint Committee on Cancer cancer staging manual. Edge S, Byrd DR, Compton CC, et al, editors. AJCC Cancer staging manual, 7th ed, XV. Springer; 2010. 649 p.

TABLE 2. Information regarding dysphagia scores and follow-up of study patients

Patient	Baseline dysphagia score	Dysphagia score follow-up week 1	Mean dysphagia score during follow-up	Follow-up, d (reason end of follow-up)
1	Liquids (3)	Some solids (1)	1	114 (surgery)
2	Semi-solids (2)	Some solids (1)	0.93	134 (death*)
3	Liquids (3)	Some solids (1)	1.30	166 (placement SEMS†)
4	Semi-solids (2)	Normal diet (0)	0	106 (surgery)
5	Liquids (3)	Normal diet (0)	1.43	113 (surgery)
6	Liquids (3)	Some solids (1)	0.55	93 (surgery)
7	Liquids (3)	Normal diet (0)	1.13	121 (surgery)
8	No passage (4)	Some solids (1)	2.20	134 (palliative brachytherapy‡)
9	No passage (4)	Some solids (1)	1.08	98 (surgery)
10	Liquids (3)	Semi-solids (2)	1.63	95 (surgery)

SEMS, Self-expandable metal stent.
*Fatal bilateral pneumonia after completion of neoadjuvant chemoradiotherapy.
†SEMS placement for a postradiation stricture at 166 days after biodegradable stent placement.
‡Single-dose brachytherapy for palliation of dysphagia due to a recurrent malignant stricture at 134 days after biodegradable stent placement.

Study outcomes

There was no 30-day mortality, and there were no intervention-related serious adverse events. Technical and clinical success rates were 100% each. Mean dysphagia score during total follow-up improved significantly compared with the baseline dysphagia score ($P < .001$) (Table 2). Weight loss occurred in 9 patients at the end of follow-up, with a median of 5.4 kg (range 0.2-11.0 kg) (relative weight loss 6.5% [range 0.4-18.8%]). In 7 of these patients, nutritional support (nasoduodenal feeding tube [n = 6], total parenteral feeding [n = 1]) was started at a median of 47 days (range 7-82 days) after stent placement. One patient had a weight gain of 2.6 kg (4.2%) at the day of surgery, without any nutritional interventions.

The 30-day morbidity rate and overall adverse event rate were 60% and 70%, respectively. Retrosternal pain immediately after stent placement developed in 6 patients and persisted for a median of 12 days (range 1-57 days). One of these patients was treated with acetaminophen, 1 with a combination of acetaminophen and nonsteroidal anti-inflammatory drugs, and 4 patients required treatment with oral opiates. Stent obstruction because of necrotic tissue developed in 1 patient after 59 days, which was successfully treated with endoscopic removal of the necrotic tissue.

Nine patients completed the full 5-week course of neoadjuvant CRT. In one patient, CRT was terminated after 4 weeks because of poor clinical condition. The latter patient still underwent thoracoscopic surgery; however, esophagectomy was not performed because of intraoperative detection of pleural metastasis. Furthermore, 3 patients did not undergo surgery for fatal bilateral pneumonia after completion of CRT in 1 patient, detection of diffuse liver metastasis with positron emission tomography after completion of CRT in a second patient, and poor performance status in a third patient. One of the latter 2 patients received single-dose brachytherapy for palliation of dysphagia because of a recurrent malignant stricture at 134 days after biodegradable stent placement. The other underwent SEMS placement at 166 days for a postradiation stricture. The remaining 6 patients underwent esophagectomy, of whom 2 had a transhiatal approach (laparotomy n = 1, laparoscopy n = 1) and 4 had a transthoracic approach (conversion to laparotomy because of adhesions, n = 1; laparoscopy, n = 3). Median total follow-up was 114 days (range 93-166 days).

DISCUSSION

This prospective, feasibility study is to our knowledge the first to describe biodegradable stent placement before neoadjuvant CRT in patients with locally advanced esophageal carcinoma. We did not detect any intervention-related serious adverse events or 30-day mortality, which is in line with the results for biodegradable stent placement in benign esophageal strictures.[8,9] In contrast, in a study by Krokidis et al,[12] two tracheoesophageal fistulas were reported after biodegradable stent placement in a heterogeneous population of 11 patients undergoing either neoadjuvant chemotherapy or radical radiotherapy. Furthermore, a study investigating biodegradable stent placement combined with single-dose brachytherapy for palliation of dysphagia was terminated prematurely because of a high serious adverse event rate, which consisted mainly of severe retrosternal pain, nausea, and loss

of appetite.[11] Although no association between stent diameter and retrosternal pain was found in that relatively small study, we decided to use only the smallest available stent diameter in this study, because, in our opinion, diameter could not be excluded as a factor. Still, moderate retrosternal pain was observed in 6 of 10 patients directly after biodegradable stent placement. Although retrosternal pain is frequently encountered after esophageal stent placement, this normally resolves within 48 hours.[13] However, in 4 patients, pain persisted for >10 days. One could speculate whether the relatively high axial force and low flexibility of the biodegradable stent[14] in combination with tissue reaction to stent disintegration and radiotherapy induce prolonged pain, although prolonged, severe, stent-related pain necessitating stent removal has been described for FSEMSs and FSEPSs.[3,6]

Stent migration did not occur in this study. This is a positive finding when considering a migration rate ranging between 31% and 60% after placement of FSEMSs or FSEPSs.[3-6] Furthermore, as in other studies, biodegradable stent placement provided quick and prolonged relief of dysphagia in all patients.[3-6] However, 9 patients experienced weight loss at the end of follow-up, and 7 patients required an additional nutritional intervention because of malnutrition. Insufficient intake despite relief of dysphagia could partly be explained by tumor cachexia and anorexia as side effects of neoadjuvant CRT, although other studies did not report significant weight loss.[3-6] We also compared study patients with the 9 patients who declined participation. Baseline characteristics and follow-up duration were comparable. There was significantly more weight loss after stent placement (-6.5% [range -18.8 to 4.20] vs 0.0% [range -3.0 to 5.95]; $P = .023$), and a nonsignificant larger proportion ultimately required nutritional intervention (7/10 vs 4/9; $P = .370$) despite significantly better mean dysphagia scores during follow-up (1.1 [range 0.0-2.20] vs 1.74 [range 0.60-2.53]; $P = .021$). Therefore, it cannot be excluded that several patients reduced eating because of stent-related adverse events, in particular, pain.

Moreover, only 6 of 10 patients underwent curative surgery, because the patients were poor surgical candidates or discovery of metastasis on either restaging imaging or during surgery. This disappointing finding was even more striking in other studies, with resection rates of only 15% and 33%.[6,15] Those studies as well as ours selected patients with severe dysphagia and locally advanced tumors only, which could explain these poor results, because the resection rate after neoadjuvant CRT in the overall population is >90%.[2]

This study is limited by a small number of patients, which was partly related to difficult patient accrual. Furthermore, comparisons with the patients who declined participation should be interpreted with caution because their data were collected retrospectively, and there is no sufficient statistical power. Moreover, patients were seen by dieticians, but there was no standardized protocol dictating how and when to intervene. Finally, interesting outcomes like quality of life and perioperative morbidity were not assessed in this pilot study.

In conclusion, our study suggests that biodegradable stent placement before neoadjuvant CRT as a bridge to surgery in patients with locally advanced esophageal carcinoma is safe in terms of 30-day mortality and serious adverse events. Although biodegradable stent placement effectively treats dysphagia, it appears to hamper oral intake for a not yet clearly elucidated reason. The clinical value of this treatment modality has to be questioned in view of weight loss and need for additional nutritional intervention. Adaptations to biodegradable stent design and probably material used, resulting in lower axial force and higher flexibility, and more diligent surveillance by a dietician may overcome these problems. This needs further evaluation, preferably in a randomized study with control groups receiving no stents and other types of stents.

REFERENCES

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Esophageal and Esophagogastric Junction Cancers version 2.2013 (2014 National Comprehensive Cancer Network, Inc, All Rights Reserved). Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed February 5, 2014.
2. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med 2012;366:2074-84.
3. Adler DG, Fang J, Wong R, et al. Placement of Polyflex stents in patients with locally advanced esophageal cancer is safe and improves dysphagia during neoadjuvant therapy. Gastrointest Endosc 2009;70:614-9.
4. Siddiqui AA, Loren D, Dudnick R, et al. Expandable polyester silicon-covered stent for malignant esophageal strictures before neoadjuvant chemoradiation: a pilot study. Dig Dis Sci 2007;52:823-9.
5. Pellen MG, Sabri S, Razack A, et al. Safety and efficacy of self-expanding removable metal esophageal stents during neoadjuvant chemotherapy for resectable esophageal cancer. Dis Esophagus 2012;25:48-53.
6. Siddiqui AA, Sarkar A, Beltz S, et al. Placement of fully covered self-expandable metal stents in patients with locally advanced esophageal cancer before neoadjuvant therapy. Gastrointest Endosc 2012;76:44-51.
7. Abu Dayyeh BK, Vandamme JJ, Miller RC, et al. Esophageal self-expandable stent material and mesh grid density are the major determining factors of external beam radiation dose perturbation: results from a phantom model. Endoscopy 2013;45:42-7.
8. van Hooft JE, van Berge Henegouwen MI, Rauws EA, et al. Endoscopic treatment of benign anastomotic esophagogastric strictures with a biodegradable stent. Gastrointest Endosc 2011;73:1043-7.
9. Repici A, Vleggaar FP, Hassan C, et al. Efficacy and safety of biodegradable stents for refractory benign esophageal strictures: the BEST (Biodegradable Esophageal Stent) study. Gastrointest Endosc 2010;72:927-34.
10. Ogilvie AL, Dronfield MW, Ferguson R, et al. Palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. Gut 1982;23:1060-7.

11. Hirdes MM, van Hooft JE, Wijrdeman HK, et al. Combination of biodegradable stent placement and single-dose brachytherapy is associated with an unacceptably high complication rate in the treatment of dysphagia from esophageal cancer. Gastrointest Endosc 2012;76:267-74.
12. Krokidis M, Burke C, Spiliopoulos S, et al. The use of biodegradable stents in malignant oesophageal strictures for the treatment of dysphagia before neoadjuvant treatment or radical radiotherapy: a feasibility study. Cardiovasc Intervent Radiol 2013;36:1047-54.
13. Stewart DJ, Balamurugan R, Everitt NJ, et al. Ten-year experience of esophageal self-expanding metal stent insertion at a single institution. Dis Esophagus 2013;26:276-81.
14. Hirdes MM, Vleggaar FP, de Beule M, et al. In vitro evaluation of the radial and axial force of self-expanding esophageal stents. Endoscopy 2013;45:997-1005.
15. Griffiths EA, Gregory CJ, Pursnani KG, et al. The use of biodegradable (SX-ELLA) oesophageal stents to treat dysphagia due to benign and malignant oesophageal disease. Surg Endosc 2012;26:2367-75.